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REVIEW Article

The Long-Term Treatment of Short Bowel Syndrome

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ABSTRACT

Short bowel syndrome (SBS) is the most common cause of intestinal failure in the pediatric population. Functionally, SBS is defined as the spectrum of malabsorption features occurring after extensive surgical resection. Congenital SBS is a rare entity, with an estimated prevalence of 0.02-0.1% among all live births. The mainstay of treatment consists of parenteral nutrition and intestinal rehabilitation, comprising surgical reconstruction. The two main procedures are Longitudinal Intestinal Lengthening and Tailoring procedure (LILT) and Serial Transverse Enteroplasty Procedure (STEP). Transplantation is reserved as treatment of last resort, when intestinal rehabilitation has been unsuccessful. Short bowel syndrome is a debilitating disease, whose management stretches over the course of years. However, with the innovation of surgical techniques such as LILT and STEP, as well as advances in multidisciplinary intestinal rehabilitation centers, long-term survival rates are approaching 90%. In this review we discuss the current and future treatment options for SBS.

Keywords: short bowel syndrome, parenteral nutrition, intestinal failure, serial transverse enteroplasty, autologous intestinal reconstructive surgery, mice behavior, inhalator administration, open field test

Abbreviations:
Short Bowel Syndrome (SBS), Longitudinal Intestinal Lengthening and Tailoring Procedure (LILT), Serial Transverse Enteroplasty Procedure (STEP), Parenteral nutrition (PN), Necrotizing enterocolitis (NEC), Neonatal Intensive Care Unit (NICU),Total parenteral nutrition (TPN), Intestinal Failure-Associated Liver Disease (IFALD), Catheter-associated bloodstream infections (CABSI), End-stage liver disease (ESLD), Prothrombin time (PT time) , International normalized ratio (INR), Glucagon-like peptide 2 (GLP-2), Autologous Intestinal Reconstructive Surgery (AIRS), Gastrointestinal anastomotic (GIA), Spiral Intestinal Lengthening and Tailoring technique (SILT), Graft versus host disease (GVHD), Coxsackie-and adenovirus receptor-like membrane protein (CLMP), Tissue-engineered small intestine (TESI).

SUMMARY

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INTRODUCTION

Short bowel syndrome (SBS) is the most common cause of intestinal failure in the pediatric population [1]. Intestinal failure refers to the state of the intestine in which its inadequate surface area renders it incapable of meeting the body's needs in terms of nutrient absorption, hydroelectrolytic equilibrium and motility. These shortcomings result in the intestine's inability to promote growth, requiring parenteral nutrition (PN) in order to meet the nutritional requirements for somatic growth. Consequently, dehydration, electrolyte imbalances and failure to thrive install [2, 3].

The term "short bowel syndrome" is reserved for describing a clinical entity resulting in intestinal failure secondary to extensive intestinal resection [3]. Short bowel syndrome can be defined from several perspectives. Anatomically, SBS is consistent with residual intestinal length less than one-quarter of that predicted for gestational age. Functionally, SBS is defined as the spectrum of malabsorption features occurring after extensive surgical resection [4]. Another functional definition of SBS commonly applied is PN-dependence for a period longer than three months [5].

The etiology of SBS is divided into congenital and acquired; wherein the vast majority of cases are acquired, secondary to surgical resection [2]. Necrotizing enterocolitis (NEC) is the leading cause of intestinal resection leading to SBS in children [6]. Necrotizing enterocolitis accounts for up to 8% of all neonatal intensive care unit (NICU) admissions, in contrast to the range of 0.5 to 2 % in the case of SBS [7]. Congenital SBS is an exceedingly rare entity. Its incidence is estimated at 3-5 cases per 100,000 live births [8]. Preterm birth is a well-established risk factor of SBS. The incidence of SBS in preterm neonates is estimated at 353.7/100,000 live births compared to 3.5/100,000 live births in term neonates [9]. Short bowel syndrome is associated with significant morbidity and mortality, carrying a mortality rate of as high as 37.5 percent during the neonatal period [10].

Various treatment options are available for SBS including medical and surgical counterparts. Medical treatment comprises parenteral nutrition, hormonal agents and hormonal therapy, however parenteral nutrition is the mainstay of therapy [11]. Surgical treatment encompasses two surgical procedures termed Longitudinal Intestinal Lengthening and Tailoring procedure (LILT) and Serial Transverse Enteroplasty Procedure (STEP) and transplantation which may be an isolated intestinal transplant or a combined intestinal-liver transplant [10, 12]. Future therapy comprises a novel surgical technique called Spiral Intestinal Lengthening and Tailoring technique (SILT) [13], gene therapy targeting the CLMP protein on chromosome 11 [14] and tissue regeneration [15]. In this review we discuss the current and future treatment options for SBS.

2. Secondary Manifestations of Short Bowel Syndrome

2.1 Intestinal Failure- Associated Liver Disease

Intestinal Failure-Associated Liver Disease (IFALD), along with CABSI are major causes of morbidity and mortality in SBS. This entity is the most consistent predictor of unfavorable outcome, occurring in as many as 60% of children with SBS [16]. An estimated 16% of patients with IFALD develop end-stage liver disease (ESLD). The clinical spectrum of IFALD includes hepatic steatosis, cholestasis, cholelithiasis and hepatic fibrosis. The pathogenesis of IFALD is thought to be multifactorial; examples of influencing factors being recurrent infections or sepsis, bowel stasis and lipid infusions, which are the main contributor. Lipid infusions result in hepatic steatosis, creating a vulnerable liver, less apt of synthesizing clotting factors, paving the way towards hemorrhagic events [17]. Intestinal failure-associated liver disease manifests biologically, with elevated serum transaminases, direct hyperbilirubinemia, increased prothrombin time (PT time) and international normalized ratio (INR) and clinically with persistent sclero-tegumental jaundice and hepatomegaly [18]. If not reversed at an incipient stage, cirrhosis ensues, and ESLD becomes inevitable [19].

2.2 Catheter- Associated Bloodstream Infections

Along with IFALD, catheter-associated blood stream infections (CABSI) represent a devastating consequence of parenteral nutrition, associated with recurrent episodes of sepsis. Catheter-associated bloodstream infections account for a compelling proportion of deaths attributed to SBS [20]. Any suspicion of CABSI warrants a thorough assessment, including two blood cultures, and the patient must be started on 48 hour empiric antibiotic treatment as early as a CABSI is suspected. The indications for catheter removal encompass positive cultures on three consecutive days, evidence of fungus growth on culture and signs of hemodynamic instability [21]. A promising new therapy employed in the prevention of CABSI is ethanol lock. Ethanol has been shown to penetrate the biofilms that form on central lines. In addition, no currently know bacterium or fungus is resistant to ethanol. Widely successful, this new therapy has managed to decrease the rate of CABSI, almost five-fold, from 9.9 to 2.2 cases per 1000 catheter days [22].

2.3 Bacterial Overgrowth

Bacterial overgrowth can occur in up to 60% of children with SBS [23]. Bacterial propagation is facilitated by dilated intestinal segments, containing Gram negative microorganisms, the most frequent culprits [24, 25]. The classic complication of bacterial overgrowth is D-lactic acidosis, an anion gap-type acidosis, having the propensity to deteriorate into coma [23]. Laboratory diagnosis is confirmed by serum D-lactate assay. Treatment consists of aggressive rehydration and antibiotics targeting Gram negative anaerobes [26]. Probiotics are not indicated as supportive therapy to antibiotics in the case of bacterial overgrowth in SBS due to evidence that patients developed catheter-associated bloodstream infections [27].

2.4 Intestinal Adaptation

Intestinal adaptation refers to a compensatory mechanism in which the intestine undergoes a course of remodeling. This process may begin as early as 24-48 after birth [28]. Among the changes that occur are mucosal hypertrophy, villous hyperplasia, crypt lengthening, thickening of the muscularis propria layer, all of which ultimately result in dilation of intestinal segments. Intestinal dilation causes dysmotility, which in turn promotes stasis, resulting in bacterial overgrowth [29]. Furthermore, the effects of bacterial overgrowth may prove to be detrimental if bacterial translocation occurs, prompting systemic infection and subsequent sepsis [26].

3. Current Treatment

3.1 Supportive Treatment: Parenteral Nutrition

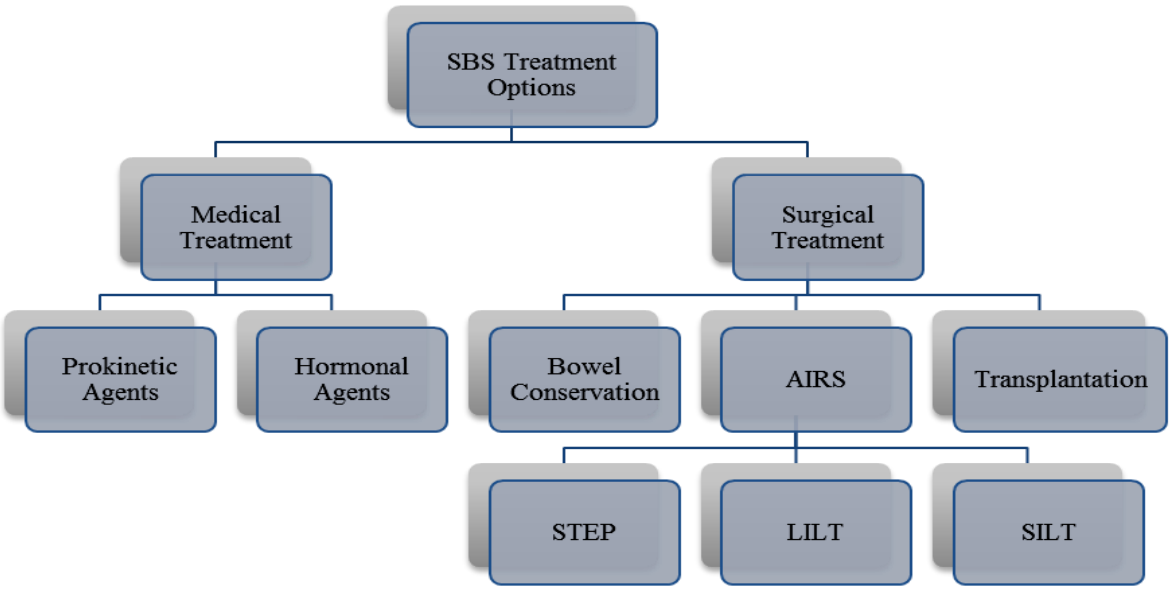

Figure 1: Short Bowel Syndrome Treatment Options

The mainstay of treatment in SBS remains nutritional support. Patients with SBS receive alimentation in the form of PN, which may be the sole mean, in this case, called total parenteral nutrition (TPN) or a mixture of PN and formula milk. The main aim of supportive treatment is to provide optimal nutrition via adequate caloric intake, and by supplementing macro and micronutrients to sustain growth and development until achieving PN independence [11.] Formulations are tailored to each patient individually. In 2008, Shin et al. in performed a study which demonstrated that soy lipid-based formulas containing omega-6 fatty acids and fish oil are effective in delaying the devastating consequences of intestinal-associated liver disease (IFALD) [30] Nonetheless, prompt transition to enteral nutrition is the desired outcome, as it eludes the risk of developing IFALD as well as catheter-associated bloodstream infections (CABSI). Although PN is a life-saving therapy in neonates with intestinal failure, it is also responsible for inducing numerous long-term complications. The most frequent complication being cholestasis, which may ultimately evolve into IFALD, requiring a combined liver- intestine transplant. Other complications include: CABSI which may lead to sepsis, bacterial overgrowth, azotemia and thromboembolic events. However, the three most common complications are IFALD, CABSI and bacterial overgrowth [31].

3.2 Prokinetic agents

Intestinal dysmotility reflects a central feature of morbidity associated with SBS. Symptoms include difficulty progressing enteral feed, vomiting and abdominal distention [32]. An article published in 2009 in the journal "Neonatology" reviewed all the randomized controlled trials performed to date on oral erythromycin administered in intermediate to high doses in preterm neonates with SBS. Findings included that erythromycin administration was associated with a 50% reduction rate in the incidence of PN-associated cholestasis as well as an equal decrease in the frequency of recurrent septicemia. Although no severe side effects were noted, long-term follow-up was the constraint of this study. Further studies are needed to evaluate the long-term outcomes [33]. The use of metoclopramide and domperidone is controversial due the potential of serious side effects. Metoclopramide induces tardive dyskinesia in up to 30% of patients [32], while domperidone is known for inducing cardiac dysrhythmia [20].

3.3 Hormonal Agents

The goal of hormonal therapy is to incite intestinal adaptation. Currently, the most promising agent available is Glucagon-like peptide 2 (GLP-2). Administration of Teduglutide has also escalated intestinal adaption, hence improving intestinal function in patients SBS [34]. Additionally, GLP-2 analogues promote villus growth [35].

3.4 Surgical Treatment

The surgical treatment options currently available include bowel conservation, autologous intestinal reconstruction surgery (AIRS) and intestinal transplantation [12]. Autologous intestinal reconstruction surgery, in turn, consists of two procedures: longitudinal intestinal lengthening and tailoring (LILT) and serial transverse enteroplasty (STEP) [10]. The aims of surgical intervention are to enhance intestinal adaptation, augment the chances of achieving enteral autonomy, and to improve quality of life for both patients and their parents [15].

3.5 Bowel Conservation

Bowel conservation refers to the surgical procedure performed at the first hospital admission. As the name suggests, the goal of this operation is to limit the amount of intestinal resection as much as possible, limited to excision of necrotic intestinal tissue only. In cases where bowel viability is questioned, a "second look" operation may be performed within 24 hours. Secondary closure is used when there is a risk of abdominal compartment syndrome, caused by edematous bowel. Only after edema has subsided, is abdominal wall closure feasible. In the case that bowel continuity cannot be established at the time of bowel conservation surgery, a stoma is placed. The standard time interval between the initial procedure and re-establishing bowel continuity is six weeks [20].

3.6 Longitudinal Lengthening and Intestinal Tailoring Procedure

The longitudinal lengthening and intestinal tailoring operation (LILT) is a type of autologous intestinal reconstruction surgery first introduced by Bianchi in 1980. Essentially, the technique of this procedure is to split the intestine into two longitudinal halves, which are then longitudinally anastomosed to the rest of the patient's intestine. This procedure

achieves total mucosal preservation, however fails to increase the total absorptive surface area. Another disadvantage of this procedure is that it must be preceded by bowel dilatation [36]. The surgical outcome was a 28-100% decrease in PN dependence. However, LILT, also known as the Bianchi procedure, is a technically complex procedure; complications such as anastomotic leakage, fistula formation and anastomotic stricture are not uncommon, emphasizing the need for improved surgical techniques [37].

3.7 Serial Transverse Enteroplasty Procedure

In 2003, Kim et al. described another intestinal lengthening procedure called "Serial Transverse Enteroplasty" (STEP) in which a gastrointestinal anastomotic (GIA) stapler is sequentially applied transversally, from alternating and opposite directions, creating a zigzag pattern. In contrast to the Longitudinal Lengthening and Intestinal Tailoring (LILT) technique, STEP may be performed as a primary procedure [38]. Additional advantages include shorter operative time due to reduced technical complexity and a shorter learning curve. The most common complication encountered is anastomotic leakage, culminating in peritonitis and staple loosening, resulting in intestinal perforation. In order to avoid these potentially-deleterious events, reinforcing sutures are placed at the apex of each staple [22]. A retrospective single-center study compared the LILT and STEP procedures performed over the course of twenty-four years. Their most prominent findings concern the possibility to wean from PN and its weaning rate. The results acquired after the STEP procedure were superior in both categories. A higher weaning rate in STEP patients was achieved, namely 60% compared to 55% after LILT, and the time required to wean off PN, 4.8 months after the STEP procedure compared to 8.4 months after the Bianchi procedure. However, no differences in patient survival were noted [39]. Another compelling result obtained after the STEP procedure was an increase in postprandial Glucagon-like peptide 2 (GLP-2) levels and increased GLP-2 expression in rats, in a 2009 experiment conducted by Kaji et al. [40]. These results were further reinforced by an analysis of the United States data registry took on by Modi et al., which demonstrated that the STEP procedure had been performed safely and successfully in many centers around the world, with uneventful postoperative recovery [41].

3.8 Transplantation

Types of intestinal transplantation include isolated intestine, liver-intestine and multivisceral [42]. The first successful combined liver-intestine transplant carried out on a patient with SBS was performed in 1990 [43]. Transplantation is reserved as the treatment of last resort. Patients are referred for a transplant in the following conditions: failure of intestinal rehabilitation, no chance of weaning off PN, development of irreversible IFALD, conditions of recurrent sepsis or when central venous access sites have been exhausted [44]. The main complications occurring after transplantation comprise: rejection, graft versus host disease (GVHD), infection and post-transplant lymphoproliferative disease. The five-year survival rate of liver-intestine transplant is 81% compared to 56% after isolated intestinal transplant, as recorded by the Transplant Center at the University of Pittsburgh [45].

3.9 Prognostic Factors

Residual small intestine length is the primary prognostic factor used for assessing parenteral nutrition (PN) dependence. The inflection point above which weaning from PN may be achieved is 35 cm of small intestine [11]. A secondary prognostic factor selected for predicting PN independence is the presence of an ileocecal valve, since it is a marker for remaining ileum [23]. A third method of assessing the ability to wean from PN is measuring the serum citrulline concentration. There is a directly proportional relationship between the serum citrulline concentration and the ability to wean from PN. The cut-off value of serum citrulline under which weaning from PN is not feasible is a value less than 12 mmol/L [24].

4. Proposed and Future Therapeutic Strategies

4.1 Spiral Intestinal Lengthening and Tailoring Procedure

The newest proposed surgical procedure employed on SBS patients is the Spiral Intestinal Lengthening and Tailoring technique (SILT) proposed by Cserni in 2013. Spiral incision lines are drawn with a marking pen at an angle between 45 to 60 degrees to the longitudinal axis of each intestinal loop. The intestine is then incised on one side, the bowel is

rotated and flipped over, and the incision is completed on the opposite side. Next, the bowel is stretched longitudinally over a transluminal catheter into a longer, narrower tube. This technique is advocated to be feasible as less manipulation of the mesentery is required and it does not alter the orientation of muscle fibers, as in the STEP procedure. However, manipulation of the vasa recta is dangerous and may lead to vascular injury, threatening intestinal viability [13]. Thus far, this technique has only been performed on animal models.

4.2 Gene-Targeted Therapy

The heritable basis of congenital SBS was first described by Hamilton et al. in 1969 [46], however the underlying genetic mechanism has not be elucidated until 2012 by Van der Welf et al. After performing homozygous mapping using 610,000 K single-nucleotide polymorphism arrays to analyze the genomes of five patients with congenital SBS, Van der Welf identified a mutation in the Coxsackie-and adenovirus receptor-like membrane protein (CLMP) [14]. The genetic basis of congenital SBS is that of an autosomal recessive pattern [47]. CLMP is a transmembrane protein encoded on chromosome 11 that acts as a cohesive molecule at gap junctions between enterocytes. It is hypothesized that a loss of cohesiveness between enterocytes is associated with decreased enterocyte proliferation [12, 14, 48]. Gene-targeted therapy represents a promising therapeutic option for congenital SBS. Furthermore, targeting the mutation in the CLMP protein on chromosome 11 will not only improve the disease prognosis, but also has potential for prenatal diagnosis in addition to genetic counseling [14].

4.3 Tissue Regeneration

The future of SBS therapy may lie in an artificially grown and harvested intestine [15]. Tissue bioengineering techniques first aroused researchers' interest in the 1988 when Vacanti et al. performed a pioneering study describing a method in which cell preparations are attached to biodegradable artificial polymers in organ culture, forming a scaffold, which is then implanted into animals[49]. Choi et al. demonstrated that tissue-engineered small intestine (TESI) is a feasible treatment option for SBS by implanting intestinal epithelial cells seeded on a polyglycolic acid matrix into rats that had undergone resection of 85% of their native intestine. The animals improved in weight gain, while histopathological analysis of the neointestine showed neomucosa formation complete with both Paneth and goblet cells [50]. Thus far, TESI has yielded promising results in animal models; however no studies have been conducted on humans [51].

5. Conclusions

Congenital SBS is a disease with high morbidity and mortality, [10] representing the main cause of intestinal failure in the pediatric population [1]. Mortality in this disease has a bimodal distribution: complications in the early post-operative period or intestinal failure-associated liver disease and catheter-associated bloodstream infections in the long-term [20]. The mainstay of treatment of SBS is parenteral nutrition and intestinal rehabilitation [11]. If intestinal rehabilitation is unsuccessful, the last therapeutic resort is intestinal transplantation [44]. The current treatment options are depicted in **Figure 1**. Not only does SBS have potential for life-threatening complications, but also for financial burden propagated by the need for repeated and prolonged hospitalization [52].

Short bowel syndrome is a debilitating disease, whose management stretches over the course of years. The ultimate therapeutic goal is to achieve enteral autonomy. Although a laborious process, it may be achieved by combining both medical and surgical expertise. The role of psycho-social support in achieving positive outcomes should not be underestimated. Surgical staff dedication and family support are indispensable.

Management of pediatric patients with SBS is a complex, long-term process requiring a specialized multidisciplinary approach [15]. However, with the innovation of surgical techniques such as LILT and STEP, as well as advances in multidisciplinary intestinal rehabilitation centers, long-term survival rates are approaching 90% [5].

Future treatment perspectives include tissue and organ regeneration as well as gene targeting therapy. Gene therapy targeting the mutation in the CLMP protein on chromosome 11 may not only improve the disease prognosis, but also has the potential for prenatal diagnosis in addition to genetic counseling [14].

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Conflict of Interest

The authors have no conflicts of interest to disclose in relation to this work.

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